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Case report

Mechanisms of unexpected death and autopsy findings in Leigh syndrome (subacute necrotising encephalomyelopathy)

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Abstract

A 21-year-old previously-well woman who was undergoing medical investigations for problems with balance and suspected multiple sclerosis, developed a headache and breathing difficulties, and died suddenly and unexpected at home. The autopsy was unremarkable except for pulmonary and cerebral oedema. However, subsequent microscopy of the brain revealed characteristic features of Leigh syndrome with multifocal areas of astrogliosis, capillary proliferation, and parenchymal vacuolation. While Leigh syndrome is more commonly diagnosed in infancy, manifestations may occur throughout early life into adulthood. Sudden and unexpected death is a rare presentation that may be associated with cerebral necrosis and oedema. An awareness of the variable manifestations of Leigh syndrome is necessary in forensic practice as not all cases will present in a typical manner and sudden death may occur before a diagnosis has been established. The heritable nature of this condition makes accuracy of diagnosis essential.

Keywords: Leigh syndrome; Sudden death; Spongiosis; Astrocytosis; Mitochondria; Encephalomyelopathy

1. Introduction

Leigh syndrome is a progressive neurodegenerative disorder that usually manifests in infancy. The inheritance pattern is variable and the underlying genetic disorder results in deficiencies in enzymes involved in oxidative phosphorylation and the generation of adenosine triphosphate (ATP).[1,2] The clinical manifestations are protean depending on the areas of the brain that have been affected. Although Leigh syndrome is usually diagnosed during life the diagnosis may rely on identification at autopsy. Given the rarity of this condition in forensic practice the following case is reported, with an overview of possible causes of sudden and unexpected death.

2. Case report

A 21-year-old woman was admitted to hospital approximately two weeks prior to death with a viral chest infection and for the investigation of difficulty with balance. A possible diagnosis of multiple sclerosis was made, and she was allowed home for a weekend. At home she became unwell and developed a headache, with nausea and vomiting, as well as breathing difficulties. Collapse occurred that was unresponsive to attempted resuscitation.

At autopsy the body was that of a young Caucasian woman consistent in appearance with the stated age. The weight was 60 kg and the height 165 cm. External examination revealed evidence of attempted resuscitation. No abnormalities of the internal organs were identified except for cerebral swelling, with grey discoloration of the central corpus callosum and periaqueductal tissue of the midbrain. There was also pulmonary oedema. The heart was structurally unremarkable and of normal size (weight = 290 g).

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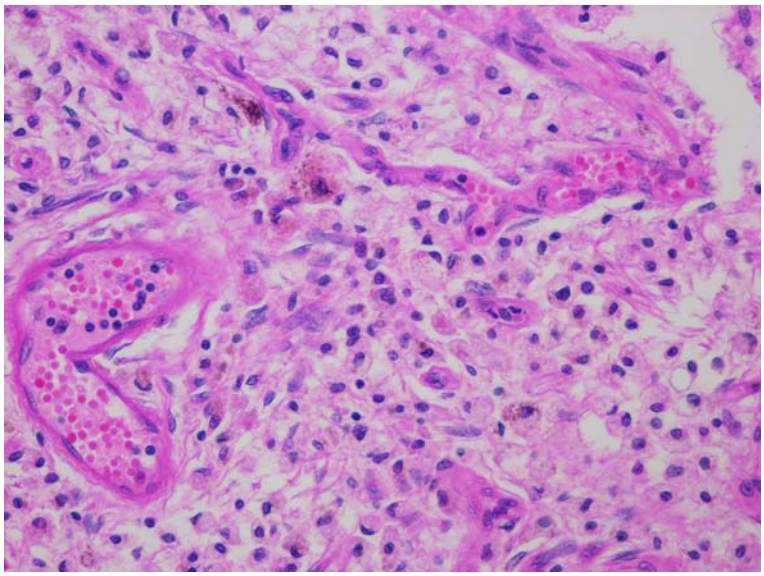

Fig. 1. Characteristic areas of vacuolation with reactive astrogliosis and relative preservation of neurones in the medulla in a case of adult-onset Leigh syndrome (Haematoxylin and eosin, 100×).

There were no pulmonary thromboemboli and there was no evidence of gastrointestinal disease.

Microscopy of the brain revealed multifocal bilateral areas of variable vacuolation, demyelinisation and astrogliosis involving the thalami, internal capsule, globus pallidus, midbrain, pons, medulla (particularly adjacent to the midline raphe), optic nerves and chiasm, corpus callosum, cingulate gyri and dentate nuclei, as well as frank necrosis with macrophage infiltration, astrogliosis and axonal swelling of most of the left substantia nigra. The mammillary bodies were normal. The findings were characteristic of subacute necrotising encephalomyelopathy (Leigh syndrome) (see Figs. 1 and 2).

Microbiological and toxicologic examinations were unremarkable and there was no evidence of trauma. No other underlying conditions were present that could have caused or contributed to death. Death was, therefore, attributed to the complications of Leigh syndrome. Three years later her 19-year-old sister also succumbed to the same condition.

3. Discussion

Leigh syndrome, or disease, was first described by Denis Leigh in 1951 in a seven-month-old boy with somnolence, blindness, deafness and spasticity who was found at

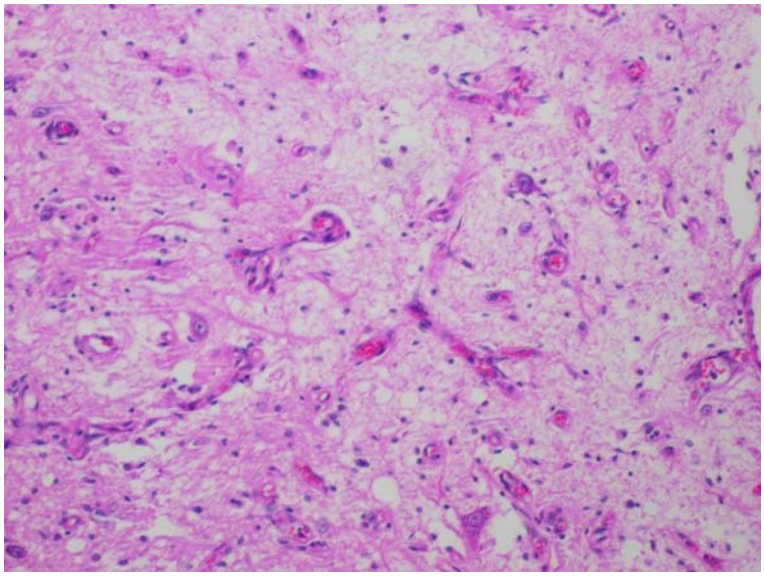

Fig. 2. Necrosis of the left substantia nigra with prominent macrophage infiltration, surrounding gliosis and axonal swelling in a case of adult-onset Leigh syndrome (Haematoxylin and eosin, 280×).

autopsy to have capillary proliferation and necrosis in his thalami, brainstem and spinal cord.[3] It is now recognised that the syndrome is a progressive degenerative disorder of the central nervous system belonging to the group of mitochondrial encephalomyelopathies that adversely affect mitochondrial energy metabolism. The most common forms are the infantile and juvenile,[4] but adult onset of the syndrome has been described. In the infantile form, symptoms appear within the first two years of life, usually after normal postnatal development, followed by developmental delay, feeding difficulties and hypotonia. The juvenile form occurs in later childhood to adolescence, and is much less common, manifesting with extrapyramidal features such as rigidity and dystonia.[4,5] Certain populations, such as in the Saguenay-Lac-Saint-Jean region of Quebec, have an increased occurrence, with an estimated incidence of one in 2063 live births, and a carrier rate of one in 23 of the cytochrome *c* oxidase deficiency type.[6]

The classical symptoms in childhood are developmental regression, ataxia and hypotonia with irregular respiration and brainstem dysfunction.[4,5] However, the clinical presentation of Leigh syndrome can be highly variable depending on the location of the affected cerebral regions.[4] Presentation of the condition in the juvenile and early adult forms may be triggered, as in the reported case, by a febrile illness.[5,7] Rarely regression of symptoms may occur.[7] Certain cases may be associated with mental retardation, spasticity and failure to thrive,[8] and facial dysmorphism, if present, requires careful photographic documentation at autopsy. Other organs apart from the brain may be involved and include the liver, kidneys, and heart.[9,10] Lactate levels may be raised in the blood and cerebrospinal fluid.[5,9] Presentations may, as in this report, be initially confused with multiple sclerosis.[11]

Leigh syndrome shows extreme genetic heterogeneity with mutations in both mitochondrial and nuclear DNA resulting in a range of deficiencies in enzymes involved in oxidative phosphorylation.[1,2,12] While the primary defect in many cases is deficiency in cytochrome *c* oxidase (complex IV; COX), deficiencies have been reported in pyruvate dehydrogenase, NADH-ubiquinone oxidoreductase (Complex I) and ATP synthase.[2,4,13] Cases may be X-linked recessive or autosomal recessive, or may occur through maternal mitochondrial inheritance, or may be sporadic.[9] Mutations have been identified in the mitochondrial MTATP6 gene and PDHA1, with defects in complex I and IV.[2] While it has been suggested that adult-onset cases are sporadic[11] the occurrence of the same condition in the sister of the decedent described in this report indicates heritability.

Death in patients with an established diagnosis of Leigh syndrome may be anticipated. However, rare cases may present with rapid deterioration and death before a diagnosis has been made, and sudden death in infancy and childhood is recognised.[14] It is these cases that present a forensic challenge. The French–Canadian type of Leigh syndrome represents a subset where there is a high mortality rate due to episodes of marked metabolic acidosis that result in coma and death.[6] Brainstem involvement may affect cardiorespiratory centres as was likely in the reported case[4,10,15] and complications of epilepsy and hypertrophic cardiomyopathy may also result in rapid death[13] (possible causes of death are summarised in Table 1).

Table 1
Possible factors involved in sudden/unexpected death in Leigh syndrome

Fulminant metabolic acidosis
Cerebral necrosis/oedema
Epilepsy
(i) cardiac arrhthymia
(ii) apnoea/respiratory failure
(iii) aspiration of gastric contents
(iv) suffocation/asphyxia
(v) trauma
Hypertrophic cardiomyopathy

Table 2
Postmortem steps in the assessment of possible Leigh syndrome

Review of clinical history – ataxia, hypotonia, preceding viral illness, etc.
External examination – facial dysmorphism
Internal examination – cardiomegaly, pulmonary oedema, cerebral oedema
Formal neuropathology – characteristic bilateral lesions
Fibroblast cultures – enzyme levels
Additional tissue enzyme levels – brain, liver, muscle
Blood/tissue for DNA analyses

Postmortem diagnosis depends on integrating a variety of pieces of information as delineated in Table 2. The most significant features are focal, bilateral lesions in the thalamus, basal ganglia, cerebellum, brainstem and spinal cord with necrosis, demyelination, gliosis, spongiosis or capillary proliferation. Neuronal sparing may occur.[16] Adequate documentation of these lesions requires formal neuropathologic assessment, as it is possible with examination of the fresh brain that subtle findings of disease may be missed. The postmortem findings and clinicopathological correlation have been summarised by Vogel[10].

In conclusion, Leigh syndrome is a rare disorder that may present as sudden and unexpected death in infants, children and adults. Inheritance patterns and clinical symptomatology are variable, and mechanisms of death may be cardiac, neurological or metabolic. Formal neuropathological evaluation is required to establish the diagnosis, and while genetic studies may not be undertaken immediately, it is important to retain blood and tissues to enable this testing to be done if subsequently required.

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